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SCIENTIFIC OPINION

Safety and efficacy of a feed additive consisting of a tincture derived from the dried fruit of *Schisandra chinensis* (Turcz.) Baill. (omicha tincture) for poultry, horses, dogs and cats (FEFANA asbl)

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Abstract

Following a request from the European Commission, EFSA was asked to deliver a scientific opinion on the safety and efficacy of a tincture from the dried fruit of *Schisandra chinensis* (Turcz.) Baill. (omicha tincture), when used as a sensory additive in feed for horses, cats, dogs, and in feed and in water for drinking for poultry. The product is a water/ethanol (55:45 v/v) solution, with a dry matter content of not more than 4% (w/w) and a content of 0.01%–0.15% (w/w) for the sum of schisandrin and deoxyschisandrin. The Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) concluded that omicha tincture is safe at the following concentrations in complete feed: 16 mg/kg for turkeys for fattening, 12 mg/kg for chickens for fattening and other poultry for fattening or reared for laying/reproduction, 18 mg/kg for laying hens and other laying/reproductive birds, 56 mg/kg for dogs and 47 mg/kg for horses and cats. The additive is considered safe for consumers when used up to the highest safe level in feed for poultry species and horses. Omicha tincture should be considered as irritants to skin and eyes, and as dermal and respiratory sensitisers. The use of omicha tincture as a flavour in feed for poultry species and horses was not considered to be a risk to the environment. Since it was recognised that the fruit of *S. chinensis* can influence sensory properties of feedingstuffs, no further demonstration of efficacy was considered necessary for the tincture under assessment.

KEYWORDS

deoxyschisandrin, flavouring compounds, omicha tincture, safety, *Schisandra chinensis* (Turcz.) Baill., schisandrin, sensory additives

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1 | INTRODUCTION

1.1 | Background and terms of reference

Regulation (EC) No 1831/2003[1] establishes the rules governing the Community authorisation of additives for use in animal nutrition. In particular, Article 4(1) of that Regulation lays down that any person seeking authorisation for a feed additive or for a new use of feed additive shall submit an application in accordance with Article 7. In addition, Article 10(2) of that Regulation specifies that for existing products within the meaning of Article 10(1), an application shall be submitted in accordance with Article 7, within a maximum of 7 years after the entry into force of this Regulation.

The European Commission received a request from Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG)[2] for authorisation/re-evaluation of 29 additives (namely dill herb oil, dill seed extract, dill tincture, dong quai tincture, celery seed oil, celery seed extract (oleoresin), celery tincture, hares ear tincture, caraway seed oil, caraway oleoresin/extract, coriander oil, cumin oil, taiga root extract (solvent-based, sb), taiga root tincture, fennel oil, fennel tincture, common ivy extract (sb), opoponax oil, ginseng tincture, parsley oil, parsley tincture, anise oil, anise tincture, ajowan oil, *Ferula assa-foetida* oil, anise star oil, anise star tincture, anise star terpenes and omicha tincture) belonging to botanically defined group (BDG) 02 – Apiales/Austrobaileyales when used as feed additives for all animal species (category: sensory additives; functional group: flavourings). During the assessment, the applicant withdrew the application for nine additives.[3] These additives were deleted from the register of feed additives.[4] During the course of the assessment, this application was split and the present opinion covers only one out of the 20 remaining additives under application: a tincture from the dried fruit of *Schisandra chinensis* (Turcz.) Baill. (omicha tincture) for all animal species. During the assessment, the applicant requested a change in the species limiting the application for authorisation to dogs, cats, horses, poultry and game birds.[5]

The remaining 19 additives belonging to botanically defined group (BDG) 02 – Apiales/Austrobaileyales under application are assessed in separate opinions.

According to Article 7(1) of Regulation (EC) No 1831/2003, the Commission forwarded the application to the European Food Safety Authority (EFSA) as an application under Article 4(1) (authorisation of a feed additive or new use of a feed additive) and under Article 10(2) (re-evaluation of an authorised feed additive). EFSA received directly from the applicant the technical dossier in support of this application. The particulars and documents in support of the application were considered valid by EFSA as of 24 June 2019.

According to Article 8 of Regulation (EC) No 1831/2003, EFSA, after verifying the particulars and documents submitted by the applicant, shall undertake an assessment in order to determine whether the feed additive complies with the conditions laid down in Article 5. EFSA shall deliver an opinion on the safety for the target animals, consumer, user and the environment and on the efficacy of the feed additive consisting of a tincture from the dried fruit of *S. chinensis* (omicha tincture), when used under the proposed conditions of use (see Section 3.2.3).

1.2 | Additional information

A tincture from *Schisandra chinensis* (Turcz.) Baill. (omicha tincture) is currently authorised as a feed additive according to the entry in the European Union Register of Feed Additives pursuant to Regulation (EC) No 1831/2003 (2b natural products – botanically defined). It has not been assessed as a feed additive in the EU.

Schisandra fruit (Schisandrae chinensis fructus) is described in a monograph of the European Pharmacopoeia 11.0 (PhEur, 2022). It is defined as the whole, dried or steamed and dried, ripe fruit of *Schisandra chinensis* (Turcz.) Baill. with a minimum content of 0.40% of schisandrin (dried drug).

[1]Regulation (EC) No 1831/2003 of the European Parliament and of the council of 22 September 2003 on the additives for use in animal nutrition. OJ L 268, 18.10.2003, p. 29.

[2]On 13/03/2013, EFSA was informed by the applicant that the applicant company changed to FEFANA asbl, Avenue Louise 130 A, Box 1, 1050 Brussels, Belgium.

[3]Dill seed extract, celery seed extract (oleoresin), caraway oleoresin/extract, opoponax oil (27 February 2019); parsley oil, hares ear tincture, taiga root extract (sb), ajowan oil (2 April 2020); celery tincture (9 December 2020).

[4]Register of feed additives, Annex II, withdrawn by OJ L162, 10.05.2021, p. 5.

[5]On 27 October 2023, the applicant withdrew the application for certain animal species.

2 | DATA AND METHODOLOGIES

2.1 | Data

The present assessment is based on data submitted by the applicant in the form of a technical dossier[6] in support of the authorisation request for the use of omicha tincture from *S. chinensis* as a feed additive. The dossier was received on 2 February 2024 and the general information and supporting documentation is available at https://open.efsa.europa.eu/questions/EFSA-Q-2024-00061.[7]

The FEEDAP Panel used the data provided by the applicant together with data from other sources, such as previous risk assessments by EFSA or other expert bodies, peer-reviewed scientific papers, other scientific reports and experts' knowledge, to deliver the present output.

Several of the components of the tincture under assessment have been already evaluated by the FEEDAP Panel as chemically defined flavourings. The applicant submitted a written agreement to reuse the data submitted for the assessment of chemically defined flavourings (dossiers, publications and unpublished reports) for the risk assessment of preparations belonging to BDG 02, including the current one under assessment.[8]

EFSA has verified the European Union Reference Laboratory (EURL) report as it relates to the methods used for the control of the active substance/agent in animal feed. The evaluation report is related to the methods of analysis for each feed additive included in BDG 02 (Apiales and Austrobaileyales). During the assessment, the EURL issued a partial report[9] and an addendum of the report,[10] which included the additive under assessment, omicha tincture. In particular, the EURL recommended a high-performance liquid chromatography with ultraviolet detection (HPLC-UV) method based on the European Pharmacopoeia monograph 01/2009:2428 for Schisandra fruit for the quantification of the phytochemical markers schisandrin and schisandrin A (deoxyschisandrin) in omicha tincture.[11]

2.2 | Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of omicha tincture from *S. chinensis* is in line with the principles laid down in Regulation (EC) No 429/2008[12] and the relevant guidance documents: Guidance on safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements (EFSA SC, 2009), Guidance for the preparation of dossiers for sensory additives (EFSA FEEDAP Panel, 2012a), Guidance on the identity, characterisation and conditions of use of feed additives (EFSA FEEDAP Panel, 2017a), Guidance on the safety of feed additives for the target species (EFSA FEEDAP Panel, 2017b), Guidance on the assessment of the safety of feed additives for the consumer (EFSA FEEDAP Panel, 2017c), Guidance on the assessment of the safety of feed additives for the environment (EFSA FEEDAP Panel, 2019), Guidance on the assessment of the efficacy of feed additives (EFSA FEEDAP Panel, 2018), Guidance on the assessment of feed additives for the user (EFSA FEEDAP Panel, 2023), Guidance document on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals (EFSA SC, 2019a), Statement on the genotoxicity assessment of chemical mixtures (EFSA SC, 2019b), Guidance on the use of the Threshold of Toxicological Concern approach in food safety assessment (EFSA SC, 2019c).

3 | ASSESSMENT

The additive under assessment, omicha tincture, is obtained from the fruit of *Schisandra chinensis* (Turcz.) Baill. It is intended for use as a sensory additive (functional group: flavouring compounds) in feed for horses, cats, dogs, and in feed and in water for drinking for poultry. The applicant included game birds in the target species. Game birds are considered to be included under 'poultry' and will not be separately referred to in the opinion.

3.1 | Origin and extraction

Schisandra chinensis (Turcz.) Baill. is a deciduous woody vine belonging to the family Schisandraceae, native to the forests of northern China, the Russian far east and Korea. The species is dioecious although several self-fertile hybrids are known. It

[6]FEED dossier reference: FAD-2010-0221.

[7]The original application EFSA-Q-2010-01286 was split on 02/02/2024 and a new EFSA-Q-2024-00061 was generated.

[8]Technical dossier/Supplementary information/Letter dated 29/04/2021.

[9]Preparations included in the partial report: dill herb oil, dill tincture, dong quai tincture, cumin oil, fennel tincture, parsley tincture, anise tincture, star anise tincture and ferula assa-foetida oil.

[10]Preparations included in the addendum: celery seed oil, caraway seed oil, coriander oil, taiga root tincture, fennel oil, common ivy extract (sb), ginseng tincture, anise oil, anise star oil, anise star terpenes and omicha tincture.

[11]The full report is available on the EURL website: https://joint-research-centre.ec.europa.eu/publications/fad-2010-0221_en.

[12]Commission Regulation (EC) No 429/2008 of 25 April 2008 on detailed rules for the implementation of Regulation (EC) No 1831/2003 of the European Parliament and of the Council as regards the preparation and the presentation of applications and the assessment and the authorisation of feed additives. OJ L 133, 22.5.2008, p. 1.

is valued for its red cherry-like fruit which occurs in clusters and is sometimes referred to as magnolia berries or five flavour berries. The fruit may be collected from the wild or from cultivations where it is grown in a manner similar to that of the grape vine. Although the fruit is edible, it is more commonly harvested for medicinal purposes and has a long tradition of use in Russia and Asia.

The term omicha (or omija) used in this opinion is the romanised version of the Korean name for the fruit or a hot water infusion prepared from the dried fruit (omija tea).

The tincture is produced from the sun-dried fruit after cleaning by winnowing and sieving. The dried fruit is extracted for 3 weeks under ambient conditions with a water/ethanol (55:45, v/v) solvent mixture and a plant to solvent ratio of 1:5 (w/v). The tincture is recovered by pressing to separate solid and liquid phases and then clarified by filtration.

3.2 | Characterisation

3.2.1 | Characterisation of the tincture

The tincture under assessment has an average density of 984 kg/m^3 (range: 980–990 kg/m^3, five batches).[13] By specification, the product is a water/ethanol (55/45, v/v) solution, with a dry matter (DM) content of no more than 4% (w/w) and a content of 0.01%–0.15% (w/w) for the sum of schisandrin and deoxyschisandrin. The analysis of five batches demonstrated compliance with the proposed specification.

Table 1 summarises the results of the proximate analysis of five batches of the additive (origin: China) expressed as % (w/w).[14] The solvent represents on average 97.19% of the additive leaving a DM content of 2.81%.[15] The DM consists of inorganic material measured as ash (12.9%, on average) and a plant-derived organic fraction (29.3% on average), which includes lipids, protein, fibre and sugars.

TABLE 1 Proximate analysis of omicha tincture derived from the fruit of *Schisandra chinensis* (Turcz.) Baill. based on the analysis of five batches. The results are expressed as % of the tincture (w/w).

		Mean	Range
Constituent	**Method**	**% (w/w)**	**% (w/w)**
Dry matter	Gravimetry	2.81	2.47–3.26
Ash	Gravimetry	0.36	0.3–0.4
Organic fraction			
Lipids	Weibull–Stoldt	< 0.3	< 0.3
Protein	Kjeldahl	0.2	0.2
Fibre	Gravimetry	< 0.5	< 0.5
Sugars	Luff–Schoorl	0.67	< 0.5–0.8
Solvent (water/ethanol, 55/45, v/v)	Difference	97.19	96.74–97.53

The fraction of secondary metabolites was characterised in the same batches of the tincture and the results are summarised in Table 2. Phenols were determined by spectrophotometry with the Folin–Ciocalteu reagent and expressed as gallic acid equivalents.[16] Flavonoids analysed by HPLC-UV were below the limit of detection (LOD, 0.2 µg/mL) in omicha tincture.[17] Organic acids (four compounds)[18] and dibenzocyclooctadiene lignans[19] were identified (six compounds) and quantified (eight compounds) by HPLC-UV. A larger number of dibenzocyclooctadiene lignans (including 13 identified compounds and three unknown derivatives) was quantifed by gas chromatography–mass spectrometry (GC–MS), which detected the presence of several volatile compounds (mono- and sesquiterpenes) in the tincture.[20] For lignans, the analytical values obtained by GC–MS are shown in Table 2, as they include a larger number of compounds.

[13]Technical dossier/Supplementary information August 2023/Annex_IV_Schisandra_Gravitational analysis_Dry matter_Density.

[14]Technical dossier/Supplementary information August 2023/Annex_II_SIn_reply_anise_tincture_Nutritional anal+Microbiol+Dioxins.

[15]Technical dossier/Supplementary information December 2022/Annex_I_Dry matter and density.

[16]Technical dossier/Supplementary information August 2023/Annex_V_Schisanda_Total Phenols.

[17]Technical dossier/Request of clarification February 2024/Annex_II_omicha_tincture_flavonoid_LOD. Limit of detection (LOD) for flavonoids: 0.2 µg/mL; limit of quantification (LOQ): 2 µg/mL.

[18]Technical dossier/Supplementary information August 2023/Annex_VI_Schisanda_Organic Acids.

[19]Technical dossier/Supplementary information August 2023/Annex_VI_Schisanda_HPLC_ Dibenzocyclooctadiene Lignans.

[20]Technical dossier/Supplementary information August 2023/Annex_VIII_Schisanda_GC-MS.

TABLE 2 Characterisation of the fraction of secondary metabolites of omicha tincture derived from the fruit of *Schisandra chinensis* (Turcz.) Baill. based on the analysis of five batches (mean and range). The results are expressed as µg/mL of omicha tincture.

Constituent	CAS no	FLAVIS no	Mean µg/mL	Range µg/mL
Phenols (total, by photometry)	–	–	167	107–216
Dibenzocyclooctadiene lignans (GC-MS)				
Deoxyschisandrin (schisandrin A)	61281-38-7	–	304.0	73.5–489.8
Gomisin A (schisandrol B)	58546-54-6	–	231.9	14.3–351.4
Gomisin F	62956-47-2	–	134.2	29.0–218.7
Gomisin G	62956-48-3	–	21.0	19.3–22.7
Schisandrin (schisandrol A)	7432-28-2	–	240.2	12.9–353.8
Schisandrin B (γ-schisandrin)	61281-37-6	–	87.2	6.5–135.1
Schisandrin B isomer	61281-37-6	–	47.7	44.9–50.4
Schisandrin C	61301-33-5	–	8.1	6.2–10.0
Schisanhenol	69363-14-0	–	29.8	12.9–45.5
Schisantherin A (gomisin C)	58546-56-8	–	102.0	25.1–168.2
Schisantherin B (gomisin B)	58546-55-7	–	105.5	102.0–108.9
Tigloylgomisin H	66069-55-4	–	153.8	145.5–162.2
Tigloylgomisin H isomer	66069-55-4	–	25.1	23.6–26.6
Unknown	–	–	35.7	7.0–61.4
Unknown	–	–	15.5	3.5–21.9
Unknown	–	–	10.6	9.5–11.7
Total			1158.6	919.3–1379.1[a]
Organic acids (HPLC-UV)				
Quinic acid			4616	4418–4898
Malic acid	6915-15-7	08.017	2780	484–6409
Shikimic acid	110-17-8	08.025	988	710–1432
Citric acid			8540	6338–11,344
Total organic acids			15,078	12,999–19,184[a]
Total identified[b]			16,403	14,303–20,604[a]
Volatiles (GC–MS)				
α-Cadinol (CG 6)	481-34-5	–	6.18	4.30–8.12
α-Terpineol (CG 6)	98-55-5	02.014	2.31	2.31–2.31
epi-α-Bisabolol (CG 6)	76738-75-5	–	1.02	1.02[c]
1-epi-Cubenol (CG 6)	19912-67-5	–	3.77	3.58–3.96
Cubenol (CG 6)	21284-22-0	–	0.59	0.52–0.66
Eudesmol (CG 6)	51317-08-9	–	0.37	0.33–0.41
T-Muurolol (CG 6)	19912-62-0	–	15.30	0.72–27.88
Nerolidol (CG 6)	7212-44-4	02.018	0.58	0.54–0.62
4-Terpinenol (CG 6)	562-74-3	02.072	4.56	1.55–7.57
β-Acoradienol (CG 7)	149496-35-5	–	36.80	36.80[c]
12-α-Santalen-14-ol (CG 7)	115-71-9	02.217	40.08	0.51–81.62
d,l-Borneol (CG 8)	507-70-0	02.016	1.45	0.65–2.24
d,l-Isobornyl acetate (CG 8)	125-12-2	09.218	7.26	0.28–15.70
Longipinocarvone (CG 8)	–	–	40.03	36.74–44.32
Nootkatone (CG 8)	4674-50-4	07.089	47.16	10.29–96.94
Oplopenone (CG 8)	–	–	0.63	0.57–0.66
1,8-Cineole (CG 16)	470-82-6	03.001	0.41	0.41[c]
1-Isopropyl-2-methoxy-4-methylbenzene (CG 26)	1076-56-8	04.043	1.33	0.88–1.77
Cuparene (CG 31, IV)	16982-00-6	–	2.30	1.68–2.92
1-Isopropyl-4-methylbenzene (CG 31, IV)	99-87-6	01.002	0.56	0.56[c]
7,14-anhydro-Amorpha-4,9-diene (CG 31, V)	–	–	4.07	2.85–5.29

TABLE 2 (Continued)

Constituent	CAS no	FLAVIS no	Mean µg/mL	Range µg/mL
Camphene (CG 31, V)	79-92-5	01.009	0.38	0.38[c]
epi-β-Caryophyllene (CG 31, V)	68832-35-9	–	1.93	0.53–3.69
Aromadendrene epoxide isomers (CG 32)	94020-95-8	–	331.84	10.48–521.93
Unknown	–	–	55.62	52.18–59.05
Unknown sesquiterpenes	–	02.014	150.34	34.07–346.77
Total volatiles			571.03	176.72–1044.38[a]

[a]The values given for the total are the lowest and the highest values of the sum of the components in the five batches analysed.
[b]considering the sum of phenols, lignans and organic acids.
[c]Compound detected in only one batch.

The tincture was shown to contain phenols up to 0.022% (w/w)[21] (0.017% on average), accounting for 0.88% of the DM (0.62% on average). Organic acids accounted up to 1.94% (w/w) of the tincture (1.53% on average) corresponding to 59.4% of the DM (54.5% on average). When determined by HPLC-UV, dibenzocyclooctadiene lignans accounted up to 0.135% (w/w) of the tincture (0.086% on average) corresponding to 4.16% of the DM (2.99% on average). When determined by GC-MS the lignans accounted for up to 0.139% (w/w) of the tincture (0.118% on average) corresponding to 4.57% of DM (4.18% on average). The volatile mono- and sesquiterpenes accounted for up to 0.11% (w/w) of the tincture (0.058% on average) corresponding to up to 3.86% of the DM (2.19% on average).

The identified secondary metabolites (16,403 µg/mL; range: 14,303–20,604 µg/mL) accounted on average for 59.3% of the DM content of the tincture (range: 52.9%–63.8%).

The structures of selected dibenzocyclooctadiene lignans are shown in Figure 1.

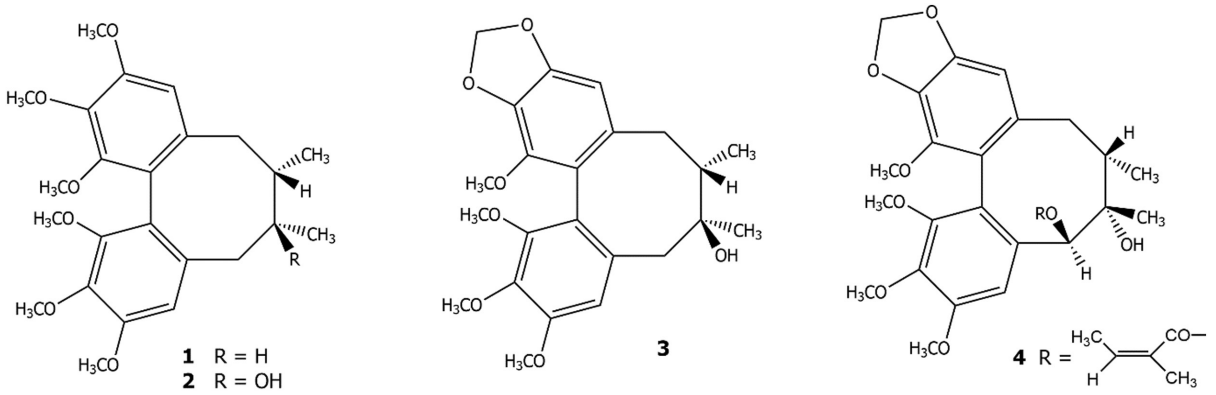

FIGURE 1 Structures of deoxyschisandrin (schisandrin A, **1**), schisandrin (schisandrol A, **2**), gomisin A (schisandrol B, **3**) and schisantherin B (gomisin B, **4**).

The applicant made a literature search (see Section 3.3) for the chemical composition of *S. chinensis* and its preparations and the identity of any recognised substances of concern.[22] The literature search retrieved 19 publications describing compositional data, none of which reported inforamtion on the presence of substances of concern is *S. chinensis* and its preparations.

The phenolic components present in the additive were not identified by the applicant. However, the Panel notes that the PhEur Commentary (2017) describes the occurrence of flavonoids such as rutin and kaempferol rutinoside in the fruit of *Schisandra chinensis* (Turcz.) Baill. In addition, for its essential oil, the monograph refers to the sesquiterpenes copaene, α-farnesene and α-cubebene as main components (PhEur Commentary, 2017).

[21]For each group of substances, the values analysed in each individual batch and expressed as µg/mL are converted into g/100 g or % (w/w) considering the value of the density determined for each individual batch. The values expressed as g/100 g are then related to the DM content determined in the corresponding batch. The values reported in the text are the average and the highest value of the range calculated for the five batches.
[22]Technical dossier/Supplementary information August 2023/Literature search_omicha_tincture.

3.2.1.1 | *Impurities*

Data on impurities were provided for three to five batches of omicha tincture.[23] Mercury and arsenic were below the corresponding limit of quantification (LOQ) in the three batches tested. Cadmium was below the LOQ in two batches and was found at 0.004 mg/kg in one batch. The concentrations of lead ranged between 0.0037 and 0.0052 mg/kg. In the same batches, mycotoxins were below the corresponding LOQ, except for mycophenolic acid which was between 8.6 and 41 µg/kg. Pesticides were not detected in a multiresidue analysis, with some exceptions. Azoxystrobin was detected in two batches between 0.013 and 0.038 mg/kg, diethyltoluamide (DEET) was detected in all three batches between 0.027 and 0.045 mg/kg, fluopicolide was detected in one batch at 0.098 mg/kg and piperonylbutoxide was detected in the three batches but was below the LOQ (0.01 mg/kg). Polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and dioxin-like polychlorinated biphenyls (PCBs) were analysed in the same batches and were below the corresponding LOQs. The calculated upper bound (UB) was 31.6 ng WHO_{2005}-PCDD/F-TEQ/kg for the sum of PCDD/Fs, and 33 ng WHO_{2005}-PCCD/F + PCB-TEQ/kg the sum of PCDD/Fs and DL-PCBs (expressed as DM).[24]

Analysis of the microbial contamination of five batches of omicha tincture showed that *Salmonella* spp. was not detected in 25 g of the batches. *Escherichia coli* was < 10 colony forming units (CFU)/g and total coliforms were not detected.[25]

The FEEDAP Panel considers that the level of microbial contamination and detected impurities do not raise safety concerns.

3.2.2 | Shelf-life

The shelf-life of the tincture is declared by the applicant to be at least 12 months when stored in tightly closed containers under standard conditions. No evidence was provided to support this claim.

3.2.3 | Conditions of use

Omicha tincture is intended for use in feed for poultry, horses, dogs and cats at maximum proposed use levels of 600, 652, 1158 and 984 mg tincture/kg complete feed, respectively.[26] The tincture is also intended for use in water for drinking for poultry. No use level has been proposed by the applicant for the use in water for drinking for poultry.

3.3 | Safety

The safety assessment of the additive is based on the highest proposed use levels in complete feed.

Several volatile components of the tincture have been already assessed as chemically defined flavourings for use in feed and food by the FEEDAP Panel, the EFSA Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with Food (AFC) and the EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). The list of flavouring compounds currently authorised for food[27] and feed[28] uses together with the EU Flavour Information System (FLAVIS) number, the chemical group as defined in Commission Regulation (EC) No 1565/2000[29] and the corresponding EFSA opinion is given in Table 3.

[23]Technical dossier/Supplementary information August 2023/Annex_VII_Schisandra_Heavy Metals_Mycotoxins_Pesticides. LOQ: < 0.005 mg/kg for arsenic, < 0.002 mg/kg for mercury, < 0.0004 mg/kg for cadmium. LOQs for individual pesticides: 0.01–0.1 mg/kg; LOQs for mycotoxins: < 0.1 µg/kg for aflatoxins B1, B2, G1 and G2, < 1 µg/kg for ochratoxin A, < 2 µg/kg for zearalenone, α- and β-zearalenone, HT2-toxin, T2-toxin cytochalasin E and sterigmatocystin, < 5 µg/kg for nivalenol, fusarenon X and diacetoxyscirpenol, and < 10 µg/kg for deoxynivalenol, deoxynivalenol-3-glycoside, 3-acetyldeoxynivalenol, 15-acetyldeoxynivalenol, citrinin, patulin and fumonisins B1, B2 and B3.

[24]Technical dossier/Supplementary information August 2023/Annex III_Schisandra_Nutritional Analysis_Microbiol_Dioxins. Upper bound concentrations are calculated on the assumption that all values of the different congeners below the limit of quantification are equal to the limit of quantification. TEQ = toxic equivalency factors for dioxins, furans and dioxin-like PCBs established by WHO in 2005 (Van den Berg et al., 2006).

[25]Technical dossier/Supplementary information/Annex_II_SIn_reply_anise_tincture_Nutritional Anal+Microbiol+Dioxins.

[26]Concentrations in complete feed based on the maximum proposed use levels of 5.3, 0.3 and 0.06 mL tincture/head per day for horses, dogs and cats, respectively.

[27]Commission Implementing Regulation (EU) No 872/2012 of 1 October 2012 adopting the list of flavouring substances provided for by Regulation (EC) No 2232/96 of the European Parliament and of the Council, introducing it in Annex I to Regulation (EC) No 1334/2008 of the European Parliament and of the Council and repealing Commission Regulation (EC) No 1565/2000 and Commission Decision 1999/217/EC. OJ L 267, 2.10.2012, p. 1.

[28]European Union Register of Feed Additives pursuant to Regulation (EC) No 1831/2003. Available online: https://ec.europa.eu/food/sites/food/files/safety/docs/animal-feed-eu-reg-comm_register_feed_additives_1831-03.pdf.

[29]Commission Regulation (EC) No 1565/2000 of 18 July 2000 laying down the measures necessary for the adoption of an evaluation programme in application of Regulation (EC) No 2232/96 of the European Parliament and of the Council. OJ L 1 80, 19.7.2000, p. 8.

TABLE 3 Flavouring compounds already assessed by EFSA as chemically defined flavourings, grouped according to the chemical group (CG) as defined in Commission Regulation (EC) No 1565/2000, with indication of the EU Flavour Information System (FLAVIS) number and the corresponding EFSA opinion.

CG	Chemical group	Product – EU register name (common name)	FLAVIS no	EFSA opinion,* year
06	Aliphatic, alicyclic and aromatic saturated and unsaturated tertiary alcohols and esters with esters containing tertiary alcohols ethers	α-Terpineol	02.014	2012b
		Nerolidol[a]	02.018	
		4-Terpinenol	02.072	
07	Primary alicyclic saturated and unsaturated alcohols/aldehydes/acids/acetals/esters with esters containing alicyclic alcohols	12-α-Santalen-14-ol[b]	02.217	2013a, 2013b CEF
08	Secondary alicyclic saturated and unsaturated alcohols, ketones, ketals and esters with ketals containing alicyclic alcohols or ketones and esters containing secondary alicyclic alcohols	*d,l*-Borneol[c]	02.016	2016a
		d,l-Isobornyl acetate	09.218	
		Nootkatone	07.089	
16	Aliphatic and alicyclic ethers	1,8-Cineole	03.001	2012c, 2021
26	Aromatic ethers including anisole derivatives	1-Isopropyl-2-methoxy-4-methylbenzene	04.043	2012d
31	Aliphatic and aromatic hydrocarbons and acetals containing saturated aldehydes	1-Isopropyl-4-methylbenzene (*p*-Cymene)	01.002	2015
		Camphene	01.009	2016b

*FEEDAP opinion unless otherwise indicated.

[a]A mixture of *(E)*- and *(Z)*-nerolidol was evaluated [02.018] (EFSA FEEDAP Panel, 2012a).

[b]Evaluated for use in food. According to Regulation (EC) 1565/2000, flavourings evaluated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) before 2000 are not required to be re-evaluated by EFSA.

[c]A mixture of *d,l*-isomers was evaluated (EFSA FEEDAP Panle, 2016a).

No studies to support the safety for target animals, consumers and users were performed with the additive under assessment. The applicant carried out a strcutured database searchto identify data related to the chenical composition ands the safety of preparations obtained from *S. chinensis*.[30]

Four cumulative databases (LIVIVO, NCBI, OVID and ToxInfo), 14 single databases including PubMed and Web of Science and 12 publishers' search facilities including Elsevier, Ingenta, Springer and Wiley were used. The literature search (no time limits) was conducted in August 2021 (updated in July 2023). The keywords used covered different aspects of safety and the inclusion and exclusion criteria were provided by the applicant.

The additive under assessment, omicha tincture, consists of 97.2% (w/w) of a water/ethanol mixture. The concentration of plant-derived compounds is about 2.8% (w/w) of the tincture. The dry matter included minerals (expressed as ash), protein, lipids and carbohydrates, which are not of concern and are not further considered.

Among the secondary plant metabolites, up to 1.94% (w/w) of the tincture consists of organic acids, up to 0.022% (w/w) of phenols, up to 0.14% (w/w) of dibenzocyclooctadiene lignans and up to 0.11% (w/w) of volatile compounds (see Section 3.2.1).

Non-phenolic organic acids, such as quinic acid, malic acid, shikimic acid and citric acid, are ubiquitous in food and feeds of plant origin and are not expected to raise concern for genotoxicity. They will be metabolised and excreted, mainly as carbon dioxide, and are not expected to accumulate in animal tissues and products. These compounds are not of concern at concentrations resulting from the use of the additive at the maximum proposed use level in feed and are not further considered in the assessment.

The presence of flavonoids in the phenolic fraction was excluded by analysis. Phenols were quantified but not identified. They will be assessed based on considerations at the level of the assessment group (see Section 3.3.4). These compounds are readily metabolised and excreted and are not expected to accumulate in animal tissues and products.

Eleven out of the 24 identified volatile constituents of omicha tincture have been previously assessed and considered safe for use as flavourings and are currently authorised for use in food[31] without limitations and for use in feed[32] at individual use levels higher than those resulting from the intended use of the tincture in feed. The list of the compounds already evaluated by the EFSA Panels is given in Table 3.

Thirteen additional volatile components have not been previously assessed for use as flavourings. The FEEDAP Panel notes that 11[33] of them are aliphatic mono- or sesquiterpenes structurally related to flavourings already assessed in CG 6, 8

[30]Technical dossier/Supplementary information December 2022/Literature_search_omicha_tincture.

[31]Commission Implementing Regulation (EU) No 872/2012 of 1 October 2012 adopting the list of flavouring substances provided for by Regulation (EC) No 2232/96 of the European Parliament and of the Council, introducing it in Annex I to Regulation (EC) No 1334/2008 of the European Parliament and of the Council and repealing Commission Regulation (EC) No 1565/2000 and Commission Decision 1999/217/EC. OJ L 267, 2.10.2012, p. 1.

[32]European Union Register of Feed Additives pursuant to Regulation (EC) No 1831/2003. Available online: https://ec.europa.eu/food/sites/food/files/safety/docs/animal-feed-eu-reg-comm_register_feed_additives_1831-03.pdf.

[33]α-Cadinol, epi-α-bisabolol, 1-epi-cubenol, cubenol, eudesmol, T-muurolol (CG 6); longipinocarvone and oplopenone (CG 8); cuparene, 7,14-anhydro-amorpha-4,9-diene and epi-β-caryophyllene (CG 31).

and 31 and a similar metabolic and toxicological profile is expected (EFSA FEEDAP Panel, 2012a, 2015, 2016a, 2016b). Two additional components are oxygenated compounds structurally related to compounds assessed in CG 31 (β-acoradienol is a sesquiterpene alcohol) and in CG 32 (aromadendrene epoxide). For these compounds, a similar metabolic and toxicological profile is also expected.

The following sections mainly address the dibenzocyclooctadiene lignans (e.g. deoxyschisandrin, gomisin A and schisandrin), based on the information provided by the applicant in the form of literature searches and quantitative structure–activity relationship (QSAR) analysis.

3.3.1 | Absorption, distribution, metabolism and excretion of lignans

No ADME studies were made with the additive under assessment. The literature search provided by the applicant (see Section 3.3) identified two reviews, where the kinetics and ADME studies of some dibenzocyclooctadiene lignans present in the tincture under assessment were summarised as well as of preparations from *S. chinensis* (Ko et al., 2014; Kopustinskiene & Bernatoniene, 2021). The applicant provided all the original refernces and the studies considered relevant are briefly described.

The kinetics of schisandrin B were studied in male rats after a single oral administration of the compound at the dose of 4 mg/kg bw (Zhu et al., 2013). Blood was collected up to 48 h after administration and the compound analysed in plasma by a validated ultra-fast liquid chromatography *tandem* mass spectrometry method (LOQ: 1 ng/mL). The maximum plasma concentration attained 1 h after oral administration was 65 ng/mL, and the half-life was 9.30 h. The double peaks found in the plasma concentration time curve of schisandrin B point to enterohepatic circulation of the compound. Concentrations of schisandrin B were also determined in tissues of groups of animals killed at several time points up to 8 h after administration. Schisandrin B is rapidly distributed in the organism, the highest tissue concentration was found 30 min after administration in liver (275.0 ng/g), followed by kidney (109.8 ng/g), lung (35.8 ng/g), heart (23.6 ng/g) and spleen (15.9 ng/g), showing that the absorbed schisandrin B was mainly present in the liver and the kidney.

Male and female rats were orally administered single or multiple doses of a *S. chinensis* ethanolic extract and lignans were analysed in plasma samples by a validated LC–MS/MS method (Xu et al., 2013). The extract was obtained from the market and the available composition determined by HPLC-UV was schisandrin (203.4 ± 3.1 μg/mg), gomisin A (schisandrol B, 61.7 ± 0.7 μg/mg), deoxyschisandrin (51.3 ± 0.4 μg/mg), schisandrin B (γ-schisandrin, 109.9 ± 1.3 μg/mg), schisantherin A (gomisin C, 59.5 ± 0.6 μg/mg) and schisandrin C (16.5 ± 0.1 μg/mg). All these compounds are present in the tincture under assessment.

To investigate the pharmacokinetics after single or multiple administration, rats were orally given 20 mg/kg bw of the extract once or twice a day for 7 days. Based on the concentrations of the lignans in the extract, the dose of 20 mg/kg bw contained 4.1 mg/kg bw schisandrin, 1.2 mg/kg bw gomisin A (schisandrol B), 1.0 mg/kg bw deoxyschisandrin, 2.2 mg/kg bw schisandrin B (γ-schisandrin), 1.2 mg/kg bw schisantherin A (gomisin C) and 0.33 mg/kg schisandrin C. Blood was collected on day 1, 5, 6 and 7 at the start of the application and at 0.17, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10 and 12 h after administration on day 1 and day 7.

The kinetic parameters of schisandrin, gomisin A (schisandrol B), deoxyschisandrin, schisandrin B (γ-schisandrin) and schisantherin A (gomisin C) were significantly different between male and female rats. The $t_{1/2}$ of all analysed lignans in female rats were two to nine times longer than the corresponding values in male. Except for schisantherin A in female rats, the C_{max} and area under the concentration–time curve from dosing (time 0) to time t (AUC_{0-t}) of the lignans were 5–50 times higher than those in male rats. The pharmacokinetic parameters determined after multiple doses showed a similar profile of those obtained after single dose. The highest difference in $t_{1/2}$ was found for deoxyschisandrin, which was five and nine times higher in female rats after single and multiple administration, respectively. Schisandrin C, the lignan present at the lowest concentration in the extract, showed concentrations below LOQ (5.0 ng/mL) both after single and multiple administration. The C_{max} of schisantherin A was similar in rats of both genders, although the AUC in female rats was two times higher than that in male rats. The most relevant finding of this study in rats was the significant difference between genders in the kinetic parameters of some lignans present in the tested extract; the absorption and tissue concentrations were significantly higher in female rats as compared with male for schisandrin, gomisin A (schisandrol B), deoxyschisandrin and schisandrin B (γ-schisandrin).

Wang et al. (2017) studied the kinetics of schisandrin B (as micronised particles of 10–20 μm) in rats. Three groups of male and female animals were orally given a single dose of 10, 20 or 40 mg/kg bw. Another group received by i.v. a single dose of 2 mg/kg bw. Blood was collected at several time points and plasma concentrations of schisandrin B determined by HPLC-MS/MS (LOQ: 2 ng/mL). The calculated absolute oral bioavailability of schisandrin B was about 55.0% in female and 19.3% in male rats, and AUC and plasma C_{max} concentrations were significantly higher also in females. Kinetic data of schisandrin B in this study confirm those obtained by Xu et al. (2013). Distribution of schisandrin B was evaluated in the rats orally given 20 mg/kg bw. Samples analysed were blood, heart, liver, spleen, lung, kidney, stomach, small intestine, large intestine, testis/ovary, muscle, brain and adipose tissue of groups of animals killed at several times up to 24 h. Peak concentrations in tissues were achieved at about 2 h after administration. In males, the highest concentrations were present in adipose tissue at any time (10 and 4 μg/g at 8 and 24 h, respectively), followed by stomach and intestine; in all the other tissues/organs, the levels were lower, about 0.2 μg/g. In females, the highest concentrations were found in ovary and adipose tissue at similar levels, about 10 μg/g at any time point. In all the other tissue/organs, the concentrations were from two to five times higher as compared with males. Data showed that schisandrin B was extensively distributed. Excretion

was evaluated by quantifying the compound in bile, urine and faeces. A very low percentage of administered compound was excreted in urine, bile and faeces. Although not analysed, the authors hypothesised that the compound would be essentially excreted as metabolites.

S. chinensis pharmaceutical products (complete composition not available) were given by gavage to male rats at 3 g/kg bw or 10 g/kg bw (Li et al., 2018). The C_{max} of schisandrin in plasma analysed by HPLC-MS/MS (LOQ: 5 ng/mL) was 80 and 150 ng/kg, respectively. The bioavailability of schisandrin was evaluated when given as single compound or in the herbal products (schisandrin 10 mg/kg bw, i.v. or 10 mg/kg bw p.o.), and the herbal extract of *S. chinensis* (3 g/kg bw or 10 g/kg bw, p.o., corresponding to schisandrin 5.2 mg/kg bw or 17.3 mg/kg bw, respectively). The bioavailability of schisandrin given alone was approximately 16%, being higher (38%) when administered in the extract. Plasma T_{max} was about 20 min for single schisandrin and 10 times higher when administered in the extract. C_{max} and AUC were 2.5 and 5 times higher for the extract as compared with isolated schisandrin. However, $t_{1/2}$ was about 1 h and similar among groups.

The metabolism of gomisin A (schisandrol B) was studied in male rats after oral administration of 250 mg/kg bw of the compound (Ikeya et al., 1990). Bile and urine were collected for 48 h and submitted to enzymatic hydrolysis. The compounds present in the extracts were separated by preparative thin layer chromatography and the pure compounds identified by nuclear magnetic resonance (NMR) and mass spectrometry. Seven metabolites were identified in bile and eight in urine. Metabolic pathways as demethylation, demethylenation and conjugation of the hydroxyl metabolites were identified.

The metabolism of schisandrin was studied in vitro and in vivo (Yan-Yan & Mu-Zou, 1993). In vitro, after incubation of schisandrin in liver microsomes of rats, the metabolites 7,8-dihydroxy-schisandrin, 7,8-dihydroxy-2-demethyl-schisandrin and 7,8-dihydroxy-3-demethyl-schizandrin were separated by preparative HPLC and identified by HPLC with diode array detector (DAD), NMR and MS analysis. In vivo the metabolism was studied in male rats after i.p. administration of schisandrin at 150 mg/kg bw; urine and bile were collected for 48 h after administration. The same metabolites were identified as those in vitro. Oxidation routes consist of hydroxylation at the alicyclic ring and demethylation at the aromatic rings.

A few studies in humans with extracts of *S. chinensis* or with its isolated lignans were also submitted.

When humans were given orally 15 mg of schisandrin, the maximum plasma concentration determined by GC-MS was about 100 ng/mL (Ono et al., 1995).

Iwata et al. (2004) incubated human liver microsomes and human small intestine (jejunum) microsomes with different extracts prepared with powder of *Schisandra* fruit (in water, methanol, ethyl acetate or diethyl ether). All the extracts showed a concentration-dependent inhibitory effect on the activity of cytochrome P450 3A4 (CYP3A4). Schisandrin and gomisins A, B, C, G and N isolated from extracts were incubated with five different human cytochrome P450 (CYP450) isoforms (CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4). Schisantherin B (gomisin B), schisantherin A (gomisin C) and gomisin G inhibited extensively the demethylation of erythromycin catalysed by CYP3A4. The inhibition caused by schisantherin A (gomisin C) showed to be irreversible. Other components also showed enzymatic inhibitory actions, although at a lower extent. Similar inhibition effects were also found for schisandrol A and gomisin A when incubated with CYP3A4 (Wan et al., 2010). In vivo data to confirm this inhibition in humans and target animals are not available.

From studies carried out in the rat with dibenzocyclooctadiene lignans, it appears that their bioavailability, both when administered isolated or in the form of extracts, is gender dependent, significantly higher in females. Lignans are rapidly absorbed and broadly distributed in the organism, mainly in adipose tissue and possibly concentrated in ovary as shown for Schisandrin B. Excretion of some isolated lignans is low, both in urine and faeces, pointing to extensive biotransformation and elimination as metabolites. The molecules have characteristics that enable to foresee extensive oxidation by demethylation, demethylenation and/or hydroxylation making them prone to conjugation and excretion. Some in vitro and in vivo studies demonstrate the formation of metabolites resulting from these metabolic pathways. Inhibition of the CYP3A4 enzyme was demonstrated in human liver and intestine microsomes both for extracts of *S. chinensis* and for some isolated lignans.

No ADME data of lignans in in the target species were made available. Considering the in vivo experimental data in laboratory animals, the FEEDAP Panel assumes that, in the target species, these compounds are rapidly absorbed, metabolised and excreted, and are not expected to accumulate in animal tissues. An exception is for cats that have limited ability to glucuronide conjugation of compounds (Court & Greenblatt, 1997; Lautz et al., 2021).

3.3.2 | Toxicology

3.3.2.1 | *Genotoxicity*

For mixtures containing a substantial fraction of unidentified components, the EFSA Scientific Committee (EFSA SC) recommends that first the chemically defined substances are assessed individually for their potential genotoxicity using all available information, including read-across and QSAR considerations about their genotoxic potential (EFSA SC, 2019b). Therefore, the potential genotoxicity of identified constituents is first considered. Then, in vitro and in vivo genotoxicity studies performed with *Schisandra chinensis* (Turcz.) Baill. extracts similar to the additive under assessment are taken into account, if deemed relevant.

The genotoxic potential for the 11 dibenzocyclooctadiene lignans identified (deoxyschisandrin, gomisin A, gomisin F, gomisin G, schisandrin, schisandrin B, schisandrin C, schisanhenol, schisantherin A, schisantherin B and tigloylgomisin H) was

predicted using the QSAR Toolbox.[34] Structural alerts were found for all the compounds and predictions of Ames mutagenicity (with and without S9) were made by 'read-across' analyses of data available for similar substances (i.e. analogues obtained by categorisation). Categories were defined using general mechanistic and endpoint profilers as well as empirical profilers. Mutagenicity read-across-based predictions were found to be consistently negative for all categories of analogues.

The literature search provided by the applicant (see Section 3.3) identified several publications on the genotoxicity of preparations obtained from *S. chinensis*. The studies considered relevant for the assessment of the genotoxic potential of these preparations were evaluated by the FEEDAP Panel and reported below.

The potential to induce gene mutations of water and ethanol extracts of the crude fruit of *Schisandra chinensis* Baill. was evaluated by an Ames test in Salmonella Typhimurium strains (TA98, TA100) and the rec-assay in *Bacillus subtilis* strains H17 Rec+ and M45 Rec–. Negative results were obtained in both assays at any concentration tested (1, 2, 5, 10 mg/plate) (Morimoto et al., 1982). No DNA fragmentation was induced in vitro by ethanol extracts from seeds of *Schisandra chinensis* (Turcz) in MCF-7 human breast cancer cell line (Li & Yang, 2018). In addition, the genotoxic potential of schisandrin B, isolated from the fruit of *S. chinensis*, was tested in vivo by a bone marrow micronucleus test and a Comet assay performed in forebrain. No significant induction of DNA damage was observed in Bal/c mice treated by gavage at 10, 25 or 50 mg/kg bw for 15 days (Giridharan et al., 2012). Negative results were also obtained for deoxyschisandrin (schisandrin A) and schisandrin B, when tested in vitro in human keratinocyte HaCaT cells by the Comet assay (Hou et al., 2015, as referenced in Nowak et al., 2019).

Overall, the available evidence indicates that preparations from *S. chinensis* or its components, the dibenzocyclooctadiene lignans, do not raise concern for genotoxicity.

3.3.2.2 | *Toxicological studies*

The literature search provided by the applicant[35] identified studies aimed at investigating several beneficial effects of *S. chinensis* and its components, the dibenzocyclooctadiene lignans.

The limited information which was available on the acute toxicity of dibenzocyclooctadiene lignans indicated that schisandrin B has a relatively higher toxicity compared to schisandrin A and C (WHO, 2007).

No subchronic toxicity studies were available that would allow the FEEDAP Panel identify a no observed adverse effect level (NOAEL).

3.3.3 | Safety for the target species

No studies to support the safety for target animals were performed with the additive under assessment.

In the absence of these data, the approach to the safety assessment of a mixture is based on its individual components or group of components (assessment groups). The combined toxicity can be predicted using the dose addition assumption within an assessment group (EFSA SC, 2019a).

The safety assessment is based on phenols, dibenzocyclooctadiene lignans and on volatile compounds present in the tincture.

For the group assessment of phenolic compounds, in the absence of data, the threshold of toxicological concern (TTC) is applied to derive maximum safe feed concentrations for the whole groups in the tincture (EFSA FEEDAP Panel, 2017b). As flavonoids were not detected in the tincture, phenolic compounds were allocated to Cramer Class I.

Based on considerations related to structural and metabolic similarities, dibenzocyclooctadiene lignans were allocated to the same assessment group. In the absence of toxicological data, the TTC was applied, and the compounds were allocated to Cramer Class III.

The volatile compounds present in the tincture were allocated to seven assessment groups, corresponding to the chemical groups (CGs) 6, 7, 8, 16, 26, 31 and 32, as defined in Annex I of Regulation (EC) No 1565/2000. The allocation of the components to the (sub-)assessment groups is shown in Table 4 and in the corresponding footnote.

For hazard characterisation, each component of an assessment group was first assigned to the structural class according to the Cramer classification (Cramer et al., 1978). For some components in the assessment group, toxicological data were available to derive NOAEL values. Structural and metabolic similarity among the components in the assessment groups was assessed to explore the application of read-across. If justified, extrapolation from a known NOAEL of a component of an assessment group to the other components of the group with no available NOAEL was made. If sufficient evidence was available for members of a (sub-)assessment group, a (sub-)assessment group NOAEL was derived.

For the volatile components of the tincture, toxicological data for subchronic studies, from which NOAEL values could be derived, were available for the representative compounds in CG 6 linalool [02.013] and terpineol [02.230] (EFSA FEEDAP Panel, 2012b), *d,l*-isobornyl acetate [09.218] in CG 8 (EFSA FEEDAP Panel, 2016a), 1,8-cineole [03.001] in CG 16 (EFSA FEEDAP Panel, 2021), d-limonene [01.045] *p*-cymene [01.002] and β-caryophyllene [01.007] in CG 31 (EFSA FEEDAP Panel, 2015, 2016b).

Considering the structural and metabolic similarities in CG 6, the NOAEL of 250 mg/kg bw per day for terpineol [02.230] was extrapolated to α-terpineol [02.014], 4-terpinenol [02.072], α-cadinol, T-muurolol, epi-α-bisabolol, eudesmol,

[34]Technical dossier/Supplementary information August 2023/Annex_XIII_Schisandra_QSAR.

[35]Technical dossier/Supplementary information August 2023/Annex_XII_Schisandra_literature_*in_vivo*_studies.

1-epicubenol and cubenol, the NOAEL of 117 mg/kg bw per day for linalool [02.013] to nerolidol [02.018]. Similarly, the NOAEL for *d,l*-isobornyl acetate [09.218] was extrapolated to *d,l*-borneol [02.016] in CG 8.

The NOAEL of 222 mg/kg bw per day for the β-caryophyllene [01.007] in CG 31 was applied using read across to camphene [01.009] and epi-β-caryophyllene.

For the remaining 11 compounds,[36] toxicity studies were not available and read-across was not possible. Therefore, the TTC approach was applied (EFSA FEEDAP Panel, 2017b). These compounds were allocated to Cramer classes I (β-acoradienol, 12-α-santalen-14-ol, 1-isopropyl-2-methoxy-4-methylbenzene and cuparene), II (nootkatone) and III (oplopenone and 7,14-anhydro-amorpha-4,9-diene).

As the result of the hazard characterisation, a reference point was identified for each component in the assessment group based on the toxicity data available (NOAEL from in vivo toxicity study or read across) or from the fifth percentile of the distribution of NOAELs of the corresponding Cramer Class (i.e. 3, 0.91 and 0.15 mg/kg bw per day, respectively, for Cramer Class I, II and III compounds, Munro et al., 1996). Reference points selected for each compound are shown in Table 4.

For risk characterisation, the margin of exposure (MOE) was calculated for each component as the ratio between the reference point and the exposure. For each assessment group, the combined (total) margin of exposure (MOET) was calculated as the reciprocal of the sum of the reciprocals of the MOE of the individual substances (EFSA SC, 2019a). An MOET > 100 allowed for interspecies- and intra-individual variability (as in the default 10 × 10 uncertainty factor). The compounds resulting individually in an MOE > 50,000 were not further considered in the assessment group as their contribution to the MOE(T) is negligible. They are listed in the footnote.[37]

The approach to the safety assessment of omicha tincture for the target species is shown in Table 4. The calculations shown in Table 4 were made for chickens for fattening at the proposed use level of 600 mg tincture/kg complete feed.

TABLE 4 Compositional data, intake values, reference points, margin of exposure (MOE) for the individual components of omicha tincture classified according to assessment group and combined margin of exposure (MOET) for each assessment group.

Tincture composition			**Exposure**		**Hazard characterisation**		**Risk characterisation**	
Assessment group	**FLAVIS-No**	**Highest conc. in the tincture**	**Highest feed conc.**	**Intake[a]**	**Cramer class[b]**	**NOAEL[c]**	**MOE**	**MOET**
Constituent	**–**	**(μg/mL)**	**mg/kg**	**mg/kg bw**	**–**	**mg/kg bw**	**–**	**–**
Dibenzocyclooctadiene lignans								
Deoxyschisandrin	–	490	0.300	0.0269	III	*0.15*	6	
Gomisin A	–	351	0.213	0.0191	III	*0.15*	8	
Gomisin F	–	219	0.134	0.0120	III	*0.15*	12	
Gomisin G	–	23	0.014	0.0012	III	*0.15*	122	
Schisandrin	–	354	0.214	0.0193	III	*0.15*	8	
Schisandrin B	–	135	0.082	0.0074	III	*0.15*	20	
Schisandrin B isomer	–	50	0.031	0.0027	III	*0.15*	55	
Schisandrin C	–	10	0.006	0.0005	III	*0.15*	277	
Schisanhenol	–	45	0.028	0.0025	III	*0.15*	60	
Schisantherin A	–	168	0.103	0.0092	III	*0.15*	16	
Schisantherin B	–	109	0.067	0.0060	III	*0.15*	25	
Tigloylgomisin H	–	162	0.098	0.0088	III	*0.15*	17	
Tigloylgomisin H isomer	–	27	0.016	0.0014	III	*0.15*	104	
Unknown	–	61	0.038	0.0034	III	*0.15*	44	
Unknown	–	22	0.013	0.0012	III	*0.15*	124	
Unknown	–	12	0.007	0.0006	III	*0.15*	236	
Total lignans	–	1379	0.836	0.0750	III	*0.15*	2	
MOET								2
Volatile constituents								
CG 7								
β-Acoradienol	–	36.8	0.0225	0.0020	I	*3*	1483	
12-α-Santalen-14-ol	02.217	81.6	0.0500	0.0045	I	*3*	669	

(Continues)

[36]β-acodarienol, 12-α-santalen-14-ol (CG 7), nootkatone, oplopenone (CG 8), 1-isopropyl-2-methoxy-4-methylbenzene (CG 26), cuparene and 7,14-anhydro-amorpha-4,9-diene (CG 31).

[37]T-muurolol, α-cadinol, 4-terpinenol, 1-epicubenol α-terpineol, epi-α-bisabolol, cubenol, nerolidol and eudesmol (CG 06); *d,l*-Borneol (CG 8), 1,8-cineole (CG 16), *p*-cymene (CG 31,IV), camphene and epi-β-caryophyllene (CG 32).

TABLE 4 (Continued)

Tincture composition			Exposure		Hazard characterisation		Risk characterisation	
Assessment group	**FLAVIS-No**	**Highest conc. in the tincture**	**Highest feed conc.**	**Intake[a]**	**Cramer class[b]**	**NOAEL[c]**	**MOE**	**MOET**
Constituent	**–**	**(μg/mL)**	**mg/kg**	**mg/kg bw**	**–**	**mg/kg bw**	**–**	**–**
MOET CG 7								461
CG 8								
Isobornyl acetate	09.218	15.7	0.0095	0.0009	(I)	**15**	17,560	
Longipinocarvone	–	44.3	0.0271	0.0024	(III)	60	24,631	
Nootkatone	07.089	96.9	0.0588	0.0053	II	*0.91*	173	
Oplopenone	–	0.66	0.0004	0.0000	III	*0.15*	4135	
MOET CG 8								163
CG 26								
1-Isopropyl-2-methoxy-4-methylbenzene	04.043	1.77	0.0011	0.0001	I	*3*	31,152	
CG 31, IV								
Cuparene	–	2.92	0.0018	0.0002	I	*3*	18,693	
CG 31, V								
7,14-anhydro-Amorpha-4,9-diene	–	5.29	0.0032	0.0003	III	*0.15*	521	
CG 32								
Aromadendrene epoxide isomers	–	521.9	0.3195	0.0287	(III)	109	3800	
Unknown volatiles								
Unknown		59.05	0.0362	0.0032	III	*0.15*	46	
Unknown sesquiterpenes	–	346.77	0.2123	0.0191	III	*0.15*	8	

[a]Intake calculations for the individual components are based on the use level of 600 mg tincture/kg complete feed for chickens for fattening. The MOE for each component is calculated as the ratio of the reference point (NOAEL) to the intake. The combined margin of exposure (MOET) is calculated for each assessment group as the reciprocal of the sum of the reciprocals of the MOE of the individual substances.

[b]When a NOAEL value is available or read-across is applied, the allocation to the Cramer Class is put into parentheses.

[c]Values in **bold** refer to those components for which the NOAEL value was available, values *in italics* are the 5th percentile of the distribution of NOAELs of the corresponding Cramer Class, other values (plain text) are NOAELs extrapolated by using read-across.

As shown in Table 4, for chickens for fattening the MOET was < 100 for 'dibenzocyclooctadiene lignans' at the proposed use levels of the additive in feed (600 mg/kg complete feed). From the lowest MOET of 2 for chickens for fattening, the MOET for the assessment group 'dibenzocyclooctadiene lignans' was calculated for the other target species considering the respective daily feed intake and conditions of use. The results are summarised in Table 5.

TABLE 5 The combined margin of exposure (MOET) for the assessment group 'dibenzocyclooctadiene lignans' calculated for the different target animal categories at the proposed use level of the additive in feed.

Animal category	Default values daily feed intake (g DM/kg body weight)	Proposed use level (mg/kg complete feed)	MOET	Maximum safe use level (mg/kg complete feed)
Chicken for fattening	79	600	2	12
Laying hen	53	600	3	18
Turkey for fattening	59	600	3	16
Horse	20	652	7	47
Dog	17	1158	5	56
Cat	20	985	5	47

Table 5 shows that, for all target species, the MOET is < 100 at the proposed use levels in feed. For the target species, the maximum safe use levels in feed were calculated to ensure an MOET ≥ 100. Generally, for cats, an MOET > 500 is considered adequate, considering their unusually low capacity for glucuronidation of compounds (Court & Greenblatt, 1997; Lautz et al., 2021). Because the MOET for dibenzocyclooctadiene lignans was derived from Cramer Class III, which is already very conservative, a value of 100 seems appropriate. The maximum safe levels in feed are shown in Table 5.

For poultry species, the FEEDAP Panel considers that the use in water for drinking alone or in combination with use in feed should not exceed the daily amount that is considered safe when consumed via feed alone.

3.3.3.1 | *Conclusions on safety for the target species*

Based on the data available, the FEEDAP Panel cannot conclude on the safety of the maximum use levels proposed by the applicant. For poultry, the calculated safe concentrations in complete feed are: 16 mg/kg for turkeys for fattening, 12 mg/kg for chickens for fattening and other poultry for fattening or reared for laying/reproduction, 18 mg/kg for laying hens and other laying/reproductive birds. For the other species, the calculated safe concentrations in complete feed are 56 mg/kg for dogs and 47 mg/kg for horses and cats. At the maximum safe concentrations in feed, the potential inhibition of cytochrome P450 by lignans, present in very low concentration, is not expected to occur.

For poultry, the FEEDAP Panel considers that the use in water for drinking alone or in combination with use in feed should not exceed the daily amount that is considered safe when consumed via feed alone.

3.3.4 | Safety for the consumer

The fruit of *Schisandra chinensis* (Turcz.) Baill. is used in Traditional Chinese Medicine (PhEur Commentary, 2017).

Several of the volatile constituents of omicha tincture under assessment are currently authorised as food flavourings without limitations and have been already assessed for consumer safety when used as feed additives in animal production (see Table 3, Section 3.3).

The main constituents of omicha tincture (quinic acid, malic acid, shikimic acid and citric acid) are ubiquitous compounds naturally present in food and feed are not expected to be of concern for consumers.

No data on residues in products of animal origin were made available for any of the constituents of the tincture. Phenolic compounds, present in the additive at concentrations below the thresholds for Cramer Class I compounds will be readily metabolised and excreted and are not expected to accumulate in animal tissues and products. Experimental data show that lignans are extensively metabolised and excreted (see Section 3.3.1). The metabolic pathways elucidated both in vitro and in vivo have been identified in target species. Therefore, the target species they will be able to carry out the biotransformation of the lignans present in the additive and no residues are expected in products of animal origin.

Similarly, for the volatile compounds present in the tincture, the available data indicate that they are metabolised and rapidly excreted and are not expected to accumulate in animal tissues and products.

No safety concern would be expected for the consumer from the use of omicha tincture up to the highest safe level in feed for poultry and horses.

3.3.5 | Safety for the user

No specific data were provided by the applicant regarding the safety of the additive for users.

The applicant provided information according to Classification, Labelling and Packaging (CLP) Regulation (EC) 1272/2008[38] concerning the presence of ethanol in the tincture.[39]

The additive under assessment should be considered as an irritant to skin and eyes and presumed to be a dermal and respiratory sensitiser.

3.3.6 | Safety for the environment

S. chinensis is a native species to Eastern Asia. It was introduced in Europe as early as 1850s, where it is commonly grown for medicinal and decorative purposes.

The main components of omicha tincture (organic acids such as quinic acid, malic acid, shikimic acid and citric acid) are ubiquitous compounds naturally present in food and feed. Phenolic compounds, lignans and volatile components which are additionally present in omicha tincture are expected to be extensively metabolised and not excreted as such by the target species.

Therefore, the use of the tincture under the proposed conditions of use in animal feed is not expected to pose a risk to the environment.

[38]Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. *OJ L 353, 31.12.2008, pp. 1–1355*.

[39]Technical dossier/Supplementary information August 2023/Annex_XIV_Schisandra_MSDS. H319: moderate eye irritation; H315: skin irritation.

3.4 | Efficacy

The fruit of *S. chinensis* is known in Asia as the 'five-flavour berry' because of its unusual combination of flavours (sour, sweet, salty, spicy and bitter). The organoleptic properties of the fruit of *S. chinensis* are described in monographs (PhEur Commentary, 2017; WHO, 2007). The pulp is described to have a slight odour and sour taste, the seeds to have an aromatic odour on crushing and a pungent and slightly bitter taste (WHO, 2007).

It is recognised that the fruit of *S. chinensis* can influence sensory properties of feedingstuffs and no further demonstration of efficacy is considered necessary for the tincture under assessment.

4 | CONCLUSIONS

The calculated maximum safe concentrations of omicha tincture from *Schisandra chinensis* (Turcz.) Baill. in complete feed for poultry are: 16 mg/kg for turkeys for fattening, 12 mg/kg for chickens for fattening and other poultry for fattening or reared for laying/reproduction, 18 mg/kg for laying hens and other laying/reproductive birds. For the other species, the calculated safe concentrations in complete feed are 56 mg/kg for dogs and 47 mg/kg for horses and cats.

For poultry species, the FEEDAP Panel considers that the use in water for drinking alone or in combination with use in feed should not exceed the daily amount that is considered safe when consumed via feed alone.

The additive is considered safe for consumers when used up to the highest safe level in feed for poultry species and horses.

The additive under assessment should be considered as irritant to skin and eyes, and as a skin and respiratory sensitiser.

The use of omicha tincture as a flavour in feed is not considered to be a risk to the environment.

Since it is recognised that the fruit of *S. chinensis* can influence sensory properties of feedingstuffs, no further demonstration of efficacy is considered necessary for omicha tincture.

5 | DOCUMENTATION PROVIDED TO EFSA/CHRONOLOGY

Date	Event
28/10/2010	Dossier received by EFSA. Botanically defined flavourings from Botanical Group 02 – Apiales and Austrobaileyales for all animal species and categories. Submitted by Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG)
09/11/2010	Reception mandate from the European Commission
26/02/2013	EFSA informed the applicant (EFSA ref. 7150727) that, in view of the workload, the evaluation of applications on feed flavourings would be re-organised by giving priority to the assessment of the chemically defined feed flavourings, as agreed with the European Commission
24/06/2015	Technical hearing during risk assessment with the applicant according to the "EFSA's Catalogue of support initiatives during the life-cycle of applications for regulated products": data requirement for the risk assessment of botanicals
27/02/2019	Partial withdrawal by applicant (EC was informed) for the following additives: dill seed extract, celery seed extract (oleoresin), caraway oleoresin/extract, and opoponax oil
24/06/2019	Application validated by EFSA – Start of the scientific assessment
03/07/2019	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. *Issues: characterization, safety for the target species, safety for the consumer, safety for the user, safety for the environment*
30/09/2019	Comments received from Member States
02/04/2020	Partial withdrawal by applicant (EC was informed) for the following additives: parsley oil, hares ear tincture, taiga root extract (sb), ajowan oil
09/12/2020	Partial withdrawal by applicant (EC was informed) for the following additives: celery tincture
31/10/2022	Reception of the Evaluation report of the European Union Reference Laboratory for Feed Additives – partial report related to nine additives (*dill herb oil, dill tincture, dong quai tincture, cumin oil, fennel tincture, parsley tincture, anise tincture, star anise tincture and ferula assa-foetida oil*)
16/12/2022	Reception of an addendum of the Evaluation report of the European Union Reference Laboratory for Feed Additives – final report related to 11 additives (*celery seed oil, caraway seed oil, coriander oil, taiga root tincture, fennel oil, common ivy extract (sb), ginseng tincture, anise oil, anise star oil, anise star terpenes and omicha tincture*)
31/09/2023	Reception of supplementary information from the applicant (partial submission: omicha tincture included in the present assessment)
27/10/2023	Partial withdrawal (target species). Species to be withdrawn: all animal species except horses, dogs, cats, poultry and game birds
02/02/2024	The application was split and a new EFSA-Q-2024-00061 was assigned to the additive included in the present assessment. Scientific assessment re-started for the additive included in the present assessment
23/02/2024	Reception of clarifications on BDG 02
13/03/2024	Opinion adopted by the FEEDAP Panel on omicha tincture (EFSA-Q-2024-00061). End of the Scientific assessment for the additive included in the present assessment. The assessment of other additives belonging to BDG 02 is still ongoing

ABBREVIATIONS

ADME	absorption distribution metabolism and excretion
AFC	EFSA Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with Food
AUC	area under the concentration-time curve from dosing (time 0) to time t
BDG	botanically defined group
BW	body weight
CAS	Chemical Abstracts Service
CEF	EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CFU	colony-forming unit
CG	chemical group
CLP	Classification, Labelling and Packaging
CYP450	cytochrome P450
DAD	diode array detector
DEET	diethyltoluamide
DL	dioxin-like
DM	dry matter
EEIG	European economic interest grouping
EURL	European Union Reference Laboratory
FEEDAP	EFSA Scientific Panel on Additives and Products or Substances used in Animal Feed
FEMA	Flavour and Extract Manufactures Association
FFAC	Feed Flavourings authorisation Consortium of FEFANA (EU Association of Specialty Feed Ingredients and their Mixtures)
FLAVIS	The EU Flavour Information System
GC-MS	gas chromatography-mass spectrometry
HPLC	high performance liquid chromatography
JECFA	Joint FAO/WHO Expert Committee of Food Additives
LC-MS/MS	liquid chromatography tandem mass spectrometry
LOD	limit of detection
LOQ	limit of quantification
MOE	margin of exposure
MOET	combined margin of exposure (total)
NMR	nuclear magnetic resonance
NOAEL	no observed adverse effect level
OECD	Organization for Economic Co-operation and Development
PCBs	polychlorinated biphenyls
PCDD	polychlorinated dibenzo-*p*-dioxins
PCDF	polychlorinated dibenzofurans
PhEur	European Pharmacopoeia
QSAR	Quantitative Structure–Activity Relationship
SC	EFSA Scientific Committee
TEQ	toxic equivalent
TTC	threshold of toxicological concern
UV	ultraviolet
WHO	World Health Organization

CONFLICT OF INTEREST

If you wish to access the declaration of interests of any expert contributing to an EFSA scientific assessment, please contact interestmanagement@efsa.europa.eu.

REQUESTOR

European Commission

QUESTION NUMBER

EFSA-Q-2010-01286 (new EFSA-Q-2024-00061)

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